91. (Currently amended) The method of claim ~~10~~19, wherein said first polynucleotide is a P-ethoxy oligonucleotide.

92. (Currently amended) The method of claim ~~21~~29, wherein said first oligonucleotide is a P-ethoxy oligonucleotide.

93. (Cancelled)

II. REMARKS

A. State of the Claims

By the present response, Applicants are prosecuting claims found to be free of the art, and reserve the right to continue with the prosecution of subject matter of cancelled claims in related, continuing applications.

To this end, claim 19, free of the art, has been amended to place it into independent form, and independent claim 10 has been cancelled. Similarly, claim 29, free of the art, was amended to place it into independent form as well. Claims previously dependent from claim 21 are now depending from 29. Claim 86, free of the art, has been amended as it depended from claim 57, and claim 57 has been cancelled. Similarly, claim 88, free of the art, has been placed into independent form as it depends from claim 10.

Currently, claims 11-15, 18-20, 22-25, 28-30, 44, 46, 58-65, 72-76, 79-89, and 91-92 are pending. Applicants would be pleased to cancel and reformat the claims in appropriate order if requested by the Examiner.

B. Claim Objections

Claim 66 is no longer pending and, thus, this objection is moot.

C. Double Patenting

The Action first observes that copending application USSN 09/381,747 may recite similar or overlapping inventions that could form the basis of future overlapping inventions. Since no rejections *per se* were entered, Applicants understand that no response is required. Applicants enclose a copy of the claims currently on file in that case.

D. Claim Rejections Under 35 U.S.C. §112, First Paragraph

The Action rejects claims 10-20, 44, 88, and 91 under 35 U.S.C. §112, first paragraph, taking the position that these claims should be limited to the use of a first polynucleotide which comprises at least eight *consecutive* bases *complementary to* the translation initiation site of Bcl-2 mRNA. Applicants respectfully traverse.

Applicants first observe that the Action fails to present any evidence directly relevant to to Bcl-2 antisense therapy. For example, the Far *et al.* reference, which is said to demonstrate among other things that only "a small portion of all possible antisense species against a given target sequence shows efficacy," concerns the automation of the design of more effective antisense sequences, and does not appear to provide any evidence with respect to Bcl-2 antisense *per se*. Similarly, the Braasch *et al.* article, said to demonstrate that antisense technology is not generally reliable, appears to also be silent with respect to Bcl-2 antisense therapy. The same can be said for Branch and Gewirtz *et al.* none of which appears to have any disclosure directed to

Bcl-2 antisense therapy. If the Examiner is aware of any disclosure from these references specifically concerning to Bcl-2 antisense, it is requested that such disclosure be pointed out. (The remaining reference mentioned by the Examiner in passing, Tamm *et al.*, does have a section dealing with ongoing and apparently successful clinical trials involved Bcl-2 antisense.)

In contrast to antisense in general, it appears that Bcl-2 presents a situation where antisense molecules to any portion of that gene have utility. Evidence in support of this proposition is the US patents to Reed (See, *e.g.*, U.S. Patents 5,831,066 (ref. A53); 6,040,181 (ref. A59); 5,734,033), counterparts to the Reed publication relied upon by the Examiner in connection with the prior art rejections. A large number of the Reed claims have no limitation on the nature of the Bcl-2 antisense molecule. See, for example, claim 11 of the '181 patent, which simply refers to "contacting said cancer cells with an anticode oligomer which (i) binds to pre-mRNA or mRNA expressed from said bcl-2 gene and which (ii) reduces expression of said human bcl-2 gene to inhibit growth of said cancer cells." Thus, in the specific case of Bcl-2 antisense, it appears that there is no basis for concluding that only antisense that comprise "at least eight *consecutive* bases *complementary to* the translation initiation site of Bcl-2 mRNA" are enabled. Accordingly, the Examiner is requested to reconsider and withdraw this rejection.

E. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Various of the claims have been rejected under 35 U.S.C. §112, second paragraph, for reasons as specified in the action. Applicants appreciate the examiner's providing suggestions addressing the rejections.

With respect to claims 28 and 30, these claims have been amended as recommended by the examiner. It is believed that these amendments address the rejection but have not changed the scope of the claims in any way.

Claim 66 and the claims depending from claim 66 have been cancelled.

Applicants do not understand the rejection of claim 91 as being incomplete. The Action states that the omitted elements recited in claim 31, from which claim 91 is said to depend, and that claim 31 was cancelled in a previous office action. However, Applicants note that claim 91 was added as a new claim in the Substitute Preliminary Amendment and Remarks filed December 2, 2002. In that amendment, claim 91 depended only from claim 10, not claim 31 The examiner is requested to clarify, perhaps by telephone call to the undersigned.

F. Prior Art Rejections

Applicants have reviewed the prior art rejections and determined that claims 19, 20, 29, 30, and 86-90 were found to be free of the prior art. Applicants are therefore prosecuting the subject matter of these claims for allowance. Accordingly, the prior art rejections need not be addressed in the context of this response. Applicants intend, however, to pursue the broader subject matter in the context of future continuing applications.

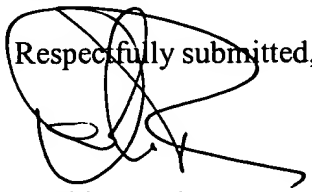
G. Conclusions

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to

any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below at (512) 536-3055.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,



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Date: March 12, 2004

PENDING CLAIMS

1. A composition comprising a P-ethoxy polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide under intracellular conditions and a neutral lipid associated with said P-ethoxy polynucleotide to form a neutrally-charged polynucleotide/lipid association.

2. The composition of claim 1, wherein said P-ethoxy polynucleotide is an oligonucleotide having a length of between about 8 and about 50 bases.

3. The composition of claim 1, wherein the P-ethoxy polynucleotide is complementary to the translation initiation site of Bcl-2 mRNA.

4. The composition of claim 3, wherein the polynucleotide is an oligonucleotide comprising the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

5. The composition of claim 1, comprising a liposome formed from the neutral lipid.

6. The composition of claim 5, wherein the P-ethoxy polynucleotide is encapsulated in the liposome.

7. The composition of claim 1, wherein the neutral lipid is a phosphatidylcholine, a phosphatidylglycerol, or a phosphatidylethanolamine.

8. The composition of claim 7, wherein the neutral lipid is dioleoylphosphatidylcholine.

9. A composition comprising an expression construct that encodes a P-ethoxy polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide under intracellular conditions, wherein said P-ethoxy polynucleotide is under the control of a promoter that is capable of expressing in eukaryotic cells, and wherein said construct is associated with a neutral lipid to form a neutrally-charged polynucleotide/lipid association.

10. A method of inhibiting a Bcl-2-associated disease comprising obtaining an antisense polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide under intracellular conditions, mixing the antisense polynucleotide with a neutral lipid to form a polynucleotide/lipid association, and administering said association to a cell, wherein said cell expresses both Bcl-2 and Bax, thereby inhibiting growth of said cell.

11. The method of claim 10, wherein the cell is a cancer cell.

12. The method of claim 11, wherein said cancer cell is a follicular lymphoma cell.

13. The method of claim 10, wherein said P-ethoxy polynucleotide is an oligonucleotide having a length of between about 8 and about 50 bases.

14. The method of claim 10, comprising a liposome formed from the neutral lipid.

15. The method of claim 14, wherein the liposome encapsulates the P-ethoxy polynucleotide.

16. The method of claim 10, wherein said contacting takes place in an animal.

17. The method of claim 16, wherein said animal is a human.

18. The method of claim 17, wherein said association is delivered to said human in a volume of 0.50-10.0 ml per dose.

19. The method of claim 17, wherein said association is delivered to said human in an amount of from about 5 to about 30 mg polynucleotide per m^2.

20. The method of claim 19, wherein said association is administered three times per week for eight weeks.

22. The composition of claim 5, wherein said liposome consists essentially of neutral lipids.

23. The composition of claim 9, comprising a liposome formed from said neutral lipid.

24. The composition of claim 23, wherein said liposome consists essentially of neutral lipids.

25. The method of claim 10, wherein said antisense polynucleotide is a P-ethoxy polynucleotide.

26. A neutral lipid oligonucleotide association comprising a neutral lipid associated with an antisense oligonucleotide of from about 8 to about 50 bases and complementary to the translation initiation site of Bcl-2 mRNA, wherein said translation initiation site comprises the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

27. The neutral lipid oligonucleotide association of claim 26, wherein the oligonucleotide has the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

28. The neutral lipid oligonucleotide association of claim 26, comprising a liposome formed from the lipid.

29. The neutral lipid oligonucleotide association of claim 28, wherein the oligonucleotide is encapsulated in the liposome.

30. The neutral lipid oligonucleotide association of claim 28, wherein said liposome consists essentially of neutral lipids.

31. The neutral lipid oligonucleotide association of claim 26, wherein the lipid is a phosphatidylcholine, a phosphatidylglycerol, or a phosphatidylethanolamine.

32. The neutral lipid oligonucleotide association of claim 31, wherein the lipid is dioleoylphosphatidylcholine.

33. A composition comprising a neutral lipid associated with an expression construct that encodes an oligonucleotide of from about 8 to about 50 bases and complementary to at least 8 bases of the translation initiation site of Bcl-2 mRNA, wherein the construct is under the control of a promoter that is capable of expressing peptides in eukaryotic cells.

34. The composition of claim 33, comprising a liposome formed from the lipid.

35. The composition of claim 34, wherein said liposome consists essentially of neutral lipids.

36. A composition comprising a first antisense polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a primary phosphatide associated with said first polynucleotide, wherein said primary phosphatide is a neutral lipid, and wherein said first polynucleotide comprises at least 8 nucleotides of the

sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1), and wherein said polynucleotide is complementary to the translation initiation site of Bcl-2.

37. The composition of claim 36, comprising a liposome formed from the primary phosphatide.

38. The composition of claim 37, wherein said liposome consists essentially of neutral lipids.

39. A method of inhibiting a Bcl-2-associated disease comprising:

a) obtaining an antisense polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide under intracellular conditions;

b) mixing the antisense polynucleotide with a neutral lipid to form a polynucleotide/lipid association; and

c) administering said association to a cell,

wherein said cell expresses both Bcl-2 and Bax, the growth of said cell is inhibited, and the non-specific toxicity of said association is less than the non-specific toxicity of the antisense polynucleotide with DMPC.

40. The method of claim 39, wherein the cell is a cancer cell.

41. The method of claim 40, wherein said cancer cell is a follicular lymphoma cell.

42. The method of claim 39, wherein said polynucleotide is an oligonucleotide having a length of between about 8 and about 50 bases.

43. The method of claim 39, comprising a liposome formed from said neutral lipid.

44. The method of claim 43, wherein the liposome encapsulates said antisense polynucleotide.

45. The method of claim 39, wherein said contacting takes place in an animal.

46. The method of claim 45, wherein said animal is a human.

47. The method of claim 46, wherein said association is delivered to said human in a volume of 0.50-10.0 ml per dose.

48. The method of claim 46, wherein said association is delivered to said human in an amount of from about 5 to about 30 mg polynucleotide per m^2.

49. The method of claim 48, wherein said association is administered three times per week for eight weeks.